

AWARD NUMBER: W81XWH-14-2-0162

TITLE: Identification and Validation of Established and Novel Biomarkers for Infections in Burns

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CONTRACTING ORGANIZATION: The University of Texas Medical Branch at Galveston Galveston, TX 77555

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14. ABSTRACT Hypothesis: Plasma proteins, clinical data, and patient characteristics can be used to prospectively identify severely burned patients who are at risk for developing sepsis and other infections. Measurement of already identified biomarkers alongside novel biomarkers identified with discovery proteomics can improve identification of risk for infection and identify the early stages of infection prior to clinical detection. This multicenter study will enable us to identify novel biomarkers, validate whether the already identified biomarkers are appropriate, and establish a predictive model. Rationale: Our prior work has shown that severely burned patients who die from sepsis can be identified via their serum protein expression profile at the time of admission, that in the days prior to septic death there is an increase in serum biomarker expression, and that the use of both clinical and proteomic information as biomarkers improves the accuracy of patient survival prediction. Others have shown that procalcitonin is a good candidate marker of sepsis in burn patients. Clinical indices such as heart rate, mean arterial pressure, base deficit, temperature, and glucose levels more accurately identify sepsis in the burn patients than does the ABA consensus definition. Methods: 200 patients will be enrolled at four sites within the Burns Research in Texas Consortia. Blood samples will be taken daily, and clinical data recorded. Specific Aims: 1. Determine plasma proteomic biomarkers for the prediction and diagnosis of sepsis using mass spectrometry techniques; use stable isotope techniques to detect proteins for which assays do not exist. 2. Validate already identified markers of infection in a multicenter study 3. Develop a model of prediction of infection using clinical data and proteomic information. Relevance: 5% of combat-sustained casualties are burn injuries; ~20% of burn patients develop sepsis. This is a life-threatening disease which needs to be treated as early as possible. The studies described here will improve clinical care for the severely burned Wounded Warriors and other burn victims.					
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1. INTRODUCTION:

Biomarkers predicting the development of sepsis and/or infections in burn patients have been proposed, but not validated. In our four site study, we are enrolling severely burned adults and children, and collecting clinical data and blood samples in order to test already proposed biomarkers of infections and sepsis. Additionally we will use novel mass spectrometry techniques to identify heretofore unidentified biomarkers of infections and/or sepsis.

2. KEYWORDS:

Sepsis, biomarkers, burns, infections, proteins, cytokines, mass spectrometry

3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals and objectives of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

- A) Protocol Development (to occur prior to subject enrollment) – completion 100%
- B) Obtain IRB approval for all four participating sites - 85% complete. HRPO has approved three sites to begin enrollment; 4th site protocol is being submitted to their IRB for review
- C) Trial Conduct (to occur once enrollment begins until final subject completes protocol) 20%
- D) Sample Analysis 15%
- E) Data Analysis (to occur following completion of data collection) 0%
- F) Maintain accurate and responsible budget – 30%
- G) Publish research data 0%

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met.

Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1. Major activities: Permission to include children in this protocol was received and the protocol submitted to the Shriners Hospitals for Children for review and approval prior to submitting the amendment to the UTMB IRB. At the USAISR, the protocol was believed to be under review by the IRB, but we found out last week that it had not been resubmitted. The PI is working with the staff at the Clinical Trials division to have this accomplished now.
2. Twenty-five patients have been enrolled to date, data collected, and samples banked. (UTMB = 13; UTHSC Houston = 7; UTSouthwestern = 5)
3. We will continue to enroll patients. IRB approval to include children in the protocol will boost enrollment rapidly.
4. A new clinical coordinator was hired at UTMB and trained to coordinate this study.

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

1. Continue to screen and enroll patients at the three approved sites
2. Continue to collect data and samples
3. Begin measuring biomarkers in the collected samples
4. Continue to work with the US-AISR to obtain IRB and HRPO approval to start screening and enrolling patients.
5. Obtain permission to enroll children at the Galveston site
6. Obtain permission for Houston to use a delayed consent

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes.

Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

1. The Shriners Hospitals for Children has reviewed the protocol – we have answered questions from their clinical research and legal divisions. I've received verbal assurance that the approval is forthcoming, which will allow submission to the UTMB IRB ; once that is approved, we will submit the paperwork to HRPO.
2. We will continue to work with the PI at the USAISR to receive approval for this protocol.
3. UTHSC-Houston submitted a request to HRPO to request permission for delayed consent at their site. We are awaiting a reply regarding this issue.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

We have delayed purchasing reagents for measuring proteins until enough samples have been accumulated. Purchases will commence now for the samples from 25 patients which we have enrolled at all sites. We had delayed purchase of the needed reagents until we had accumulated enough samples to run in batches so that we would not be stuck with reagents that expired before they could be used.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title;*

journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Investigators met at the UT Southwestern in august to discuss the protocol and status of this project. All reaffirmed support for this project and agreed to try to increase enrollment.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change.”

Example:

Name:	Mary Smith
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	1234567
Nearest person month worked:	5
Contribution to Project:	Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support:	The Ford Foundation (Complete only if the funding support is provided from other than this award).

Name:	Finnerty, Celeste
Project Role:	PD/PI
Research Identifier (e.g., ORCID ID):	not applicable
Nearest Person Month Worked:	2
Contribution to Project:	Dr. Finnerty continues to enroll patients and to begin analysis of the gathered samples. Not applicable
Funding Support:	
Name:	Steven Wolf
Project Role:	co-I
Research Identifier (e.g., ORCID ID):	not applicable
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Wolf continues to enroll patients Not applicable
Funding Support:	
Name:	Charles Wade
Project Role:	Co-I
Research Identifier (e.g., ORCID ID):	not applicable
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Wade continues to enroll patients and to pursue approval by HRPO for delayed consent. Not applicable
Funding Support:	
Name:	Julie Rizzo, MD
Project Role:	Co-I
Research Identifier (e.g., ORCID ID):	not applicable
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Rizzo is pursuing approval of the IRB protocol. Not applicable
Funding Support:	
Name:	David Herndon, MD
Project Role:	Co-I
Research Identifier (e.g., ORCID ID):	not applicable
Nearest Person Month Worked:	1
Contribution to Project:	Dr. Herndon continues to enroll patients. Not applicable

Funding Support:	Andy Kudlicki
Name:	Co-I
Project Role:	not applicable
Research Identifier (e.g., ORCID ID):	2
Nearest Person Month Worked:	Dr. Kudlicki has worked on developing the data analysis methods for this project
Contribution to Project:	Not applicable
Funding Support:	Yingxin Zhao
Name:	Co-I
Project Role:	not applicable
Research Identifier (e.g., ORCID ID):	2
Nearest Person Month Worked:	Dr. Zhou has worked on developing the mass spec analytical methods for this project
Contribution to Project:	Not applicable
Funding Support:	Heather Suhey
Name:	Assistant clinical coordinator
Project Role:	Not applicable
Research Identifier (e.g., ORCID ID):	2
Nearest Person Month Worked:	Ms. Suhey enrolls patients, obtains samples and data, submits protocol changes to the Shriners Hospitals for Children, the UTMB IRB, and HRPO, and communicates with the coordinators at the other sites.
Contribution to Project:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.